THE STATE OF QUANTITATIVE GENETICS
IN RELATION TO THE REAL WORLD

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Let me interpret the title to mean "How good are predictions of genetic change in a single environment on the basis of existing theory?"

I take the view that on the whole the theory does not do too bad a job in predicting the responses to selection pressure in the first few generations. Now the classical prediction equations of quantitative genetics can be written as follows:

\[ \Delta G = h^2 \Delta P \]

\[ \Delta G = \mathbf{h} \mathbf{c}_A \]

In using the first equation, we are then operating after the fact - predicting the amount of change from the known selection differential. But the restrictions on this equation are often not fully appreciated. In fact it is very restricted indeed. It really only applies when the selection differential has been produced by artificial selection for that particular characteristic. We cannot in any way use it in situations in which the selection differential has arisen for reasons of which we know very little. This will be immediately obvious when one considers that, in selecting for a first character, we frequently bring about what we might call a correlated selection differential in other characters because the two are phenotypically correlated. But we know that we cannot calculate the expected genetic change in these secondary characters without knowing the genetic correlation between them and the primary. The same problem arises if we consider the consequences of using a selection index containing several characters. We are then not in
a position to use simple theory for any of the components of this index. The problem is particularly important in discussing natural selection and I shall return to it later in the talk.

But I will be concerned mostly with the application of the second equation which considers the situation a priori and predicts what selection differential there is likely to be. I would rephrase my question then 'What conditions must hold for this selection prediction to apply for many generations'. I would summarise the conclusions roughly as follows:

(i) the additive genetic variation must not change during the process of selection. For this to hold two conditions must apply:

(a) As the additive genetic variance will be jointly due to the action of many loci, for the variance not to alter the change in the mean gene frequency at each locus would need to be small. The number of loci concerned would then need to be very large.

(b) The genetic variance will also change due to genetic drift - due to the decline in heterozygosity because of inbreeding. In the purely additive case, we know that a fraction $1/2N$ of the genetic variance will be lost each generation, where $N$ is the effective population size. Our present theory is an infinite population one - we have to modify it to cope with the finite populations within which selection is carried out in practice.

(ii) We must be working on the right scale. This again splits into two sections:

(a) Genetic. Here the right scale is one on which the effect of a given gene substitution is always the same. Deviations from this
can be in general summarised under the classifications of dominance and epistasis and the general problem of scale transformations may be considered as specific kinds of epistasis.

(b) Environmental. Here we must assume that the environmental variation does not change with the mean.

(iii) We have to assume that all loci are segregating independently. Under selection, it can be shown that negative linkage disequilibrium will build up between alleles at different loci affecting the character in the same direction and that this will cause a reduction in the additive genetic variance and will consequently reduce final response. I will be dealing in some detail with the problem of linkage in the second talk at this meeting.

(iv) That the effective selective differential does not alter. Here the main problem would be opposing natural selection as artificial selection proceeds as was found by Dempster and Lerner for shank length in chickens.

The problem of scale

Clearly if dominance or epistasis are at all important, predictions will quickly break-down. But there is a particular kind of epistasis, that which can be removed by a transformation, which can in some situations be dealt with. The importance of scale transformations is, of course, very dependent on the degree of variation in the character with which we are working. Scale transformations may be of little value if we are working within a segregating population with a small coefficient of variation. But if we are concerned with differences between lines produced by selection within this same population, we need to be sure that we are working on the correct scale before we can discuss the situation adequately. For instance in my usual bristle character in Drosophila,
I will not be much in error if I assume additive gene action within a segregating population whereas I have good evidence that gene action is close to multiplicative for this character. Most theoretical arguments about changes due to selection are phrased in terms of gene frequencies. An adequate scale is therefore one on which the effect of a given gene substitution is constant, irrespective of the background on which it is made. This condition we may find very difficult to verify experimentally. However, at least in Drosophila, we have the possibility of measuring the effect of a given chromosomal substitution in different backgrounds. The table which follows presents as pairs of observations the mean sternopleural bristle score of sets of flies differing in their X-chromosomes but identical in their autosomes. The two different X-chromosomes were obtained from the highest and lowest bristle lines which I have in my possession. The table shows quite clearly that the effect of this substitution is very different in a low bristle background compared to the value in a high background. Obviously any discussion of genetic changes in terms of absolute bristle score are likely to be very misleading. Of the sternopleural bristles, one generally finds that two bristles on either side of the fly are different in kind from the remainder which lends some physiological justification for deducing from the data that genes act multiplicatively on the number of bristles after the first four, i.e. that a transformation of log (S-L) will do quite a reasonable job. For reasons purely of scale the genetic variance might be then expected to increase with selection upwards and decrease with selection downwards. Superimposed upon this of course will be the effect of changes in gene frequency.
Table 1. The mean bristles scores of males having 'high' and 'low' X chromosomes in different backgrounds

(The figures in the last column have a standard error of 0.03.)

<table>
<thead>
<tr>
<th>Source of X chromosome</th>
<th>Difference</th>
<th>Absolute</th>
<th>Log(S - 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal background</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>9.49</td>
<td>7.75</td>
<td>1.74</td>
</tr>
<tr>
<td>B</td>
<td>13.34</td>
<td>10.84</td>
<td>2.50</td>
</tr>
<tr>
<td>C</td>
<td>22.72</td>
<td>16.36</td>
<td>6.36</td>
</tr>
<tr>
<td>D</td>
<td>34.87</td>
<td>24.84</td>
<td>10.03</td>
</tr>
<tr>
<td>E</td>
<td>47.80</td>
<td>32.80</td>
<td>15.00</td>
</tr>
</tbody>
</table>

The environmental variance need not necessarily remain constant on the scale which is adequate for a discussion of genetic effects. For bristles, for instance, we have evidence that the environmental variation is less affected by scale than is the additive genetic variance. As a consequence the heritability increases in the early generations of selection upwards whereas it drops quite rapidly on selection downwards. For the remainder of my talk then I must assume that we have by some means or another cleared scale problems out of the way.

The effect of population size

I said earlier that existing theory assumed that all gene effects are small and that the population size is large. We can make some predictions with finite population size but retaining the condition of small gene effects. In such a situation, changes in the additive genetic variation are due to drift and not to alterations in gene frequency from selection. The additive genetic variation then declines with time as $e^{-t/2N}$ and by integrating this over time we can show that the total response will be $2N$ times the response in the first generation. The limit will be approached gradually as the genetic variation declines and we can specify the time scale of this by saying that the population...
will get halfway to its eventual limit in $1.4N$ generations. As fixation occurs only by drift, we must then expect to find a great deal of variation between replicate lines selected in the same way. As a further consequence of this, since different genes will be fixed in different replicates, we can expect to make further response on crossing replicates at the limit and forming a new random breeding population.

If the changes of gene frequency at some loci are large during the selection process, the above figures for gain and for the half life will be upper limits. In the extreme case in which the probability of fixation of the desirable alleles at all loci is very high, there will then be no variation between replicate lines and consequently no point in crossing them.

Rather more generally it can be shown that with additive gene action and individual selection, the gain at the limit is a function of $N_i$. This has one interesting consequence. If we select from a constant number of individuals each generation, then the two components of $N_i$ will be incompatible. The more intensely we select, the lower the effective population size. In fact $N_i$ passes through a maximum when 50% of the population are selected in each generation. In fact this maximum, considered as a function of the proportion selected may be very flat indeed so that the gain at the limit will be the same over a wide range of values of proportion selected. If we are concerned to maximise gain in $t$ generations and we are using individual selection from a total of $T$ individuals, it can then be shown that the optimum proportion selected is a function of $t/T$ which approaches 0.5 as $t/T$ increases.

There has not been a great deal of experimental work on the limits to artificial selection. The main part of this is the work of Dr. J. S. F. Barker and his collaborators in Australia. Starting from a given random breeding
population, they have looked at the effect of various aspects of the selection programme, such as the effective population size and the intensity of selection and have found that the results are in reasonable agreement with the theory. Evidence of a rather more general nature comes from the fact that in the majority of selection experiments the limit to selection is reached well before one would expect on selection theory based on a very large number of loci. Again there is good evidence both with Drosophila and with mice that considerable variation between replicates is usual in selection experiments. This would argue in the opposite direction - that it is unlikely that the selection response is due to a very small number of loci with large effects. Results of a recent experiment to look into the possibility that an extreme selected line from a given base population could be further improved after back crossing to the base population would suggest that there are genes present in the base population which are not fixed in the initial selection. In our experiments we had evidence that we had missed genes on the second, third and fourth chromosomes of Drosophila. From various pieces of evidence as to the effect of various constraints on the selection limit, I have the impression that if selection is not too intense and is in the usual size of population, the response I get is from genes at intermediate gene frequencies. But if I try very hard to make use of all the useful variation in a population I find that I have earlier missed some genes with large effects, because their initial gene frequency is low.

Again working with Drosophila, Thoday and his collaborators have been able to isolate the loci responsible for selection response in bristles and to show that a large part of the response can be accounted for by changes at a small number of loci - that is to say less than 10. This impression is corroborated by
what experimental work I have done in this direction. For instance of the
difference between the high and low X-chromosomes, which I used earlier in the
discussion on scale, about one half is due to a single locus whose position I
know fairly accurately on the X-chromosome. The high alternative seems to be
very rare in our base population.

Correlated responses

Here I would draw a distinction between those correlated responses which
are likely to be linear with time, such as the changes in a metric character
not under selection, compared to those correlated responses in fitness
characteristics which are likely to increase as the square of the number of
generations. As a result of theoretical work by Bohren, Hill and myself on
changes of the genetic co-variance between two characters on selection for one
of them, I came to realise that the co-variance between two characters will be
much more sensitive to changes due to selection and due to genetic drift than
will be the variance of a single character. The variance is made of positive
contributions from the different loci - the genetic co-variance, if the correlation
is not too high, may well be made up of contributions of different sign at the
different loci. As a consequence changes in the contributions of the separate
loci due to drift and to selection will have a greater relative effect on the
co-variance than on the variance. We must therefore expect that predictions of
a correlated response will be valid over a much smaller number of generations
than are predictions of direct response and this I think is borne out by plenty
of experimental evidence. The problem of non-linear alterations of fitness
characteristics on selection for metric characters is an almost untouched field.
We have no good predictive theory and very little experimental evidence. In fact
the only good experimental evidence from domestic animals comes from the selection work carried on in chickens by Nordskog and his collaborators. They found that fitness characteristics fell on selection for egg weight and body weight in either direction and that after such selection there was a negative inter-relationship between fitness and the metric character which was not present at the start of selection. This kind of behaviour is not unexpected - if there are loci for instance with an additive effect on the metric character which are overdominant with respect to fitness we should expect the fitness to drop as selection moves the gene frequency away from its equilibrium value.

A rather more general problem involving the inter-relationship between metric and fitness characters arises when we consider the probable effect of natural selection on a metric character. Because we do not know the way in which any observed selection differential in natural selection arises we cannot then use the standard methods of calculating expected change by multiplying the selection differential by the heritability. There is however one general way in which the genetic consequences of any selection process at the individual level can be assessed. This is by what one might call the secondary theorem of natural selection. Fisher's fundamental theorem of natural selection says that the expected change in the Malthusian parameter, which is in some ways equivalent to fitness, is equal to its additive genetic variance. One can easily show that the expected change in any metric character is then equal to the additive genetic co-variance between the character and fitness. This method I have used to assess the probable genetic consequences of the culling in different lactations on milk yield in dairy cattle.

Our basic difficulty in predicting the consequences of non-linear relationships between metric characters and fitness is that these may arise from two completely
different models. On the first model we might assume that, though loci affecting
the metric character act additively, they are held in the population because of
an overdominant effect on fitness. There is then no interaction between the loci
in their effect on fitness. In the alternative optimum model, we assume that
the effect of these particular loci on fitness acts only through their effect
on a metric character and that the selective disadvantage of an individual increases
as does its deviation in the character from the population mean. This implies
that, as far as fitness is concerned, there is an interaction between loci. An
allele having a positive effect on the metric score will then be at an advantage
if there are low alternatives present at the other loci and at a disadvantage if
there are high alternatives present at the loci affecting the metric character.
On both models of course one will see a curvilinear relationship between fitness
and the metric character and on both fitness will decline on selecting the metric
character in either direction.

I have recently carried out a series of experiments with the hope of deciding
between these two alternative mechanisms. The design rests on the necessary
interaction between the loci with respect to fitness in the optimum model which I
mention earlier. I therefore looked at the effect of natural selection on the
bristle loci on the third chromosome in Drosophila in two quite different situations.
In one the first, second and fourth chromosomes were homozygous for low bristle
genes and in the other background they were homozygous for high bristle genes. If
the optimum model were true I would then expect the bristle score to increase under
natural selection in a low background and to decrease in a high background. In
both cases the mean would be coming back to the usual value in wild type populations.
I have had these populations segregating now in large population cages for
several years and I find no tendency for this to occur. The evidence is then not in favour of the optimum model.

I incautiously used the phrase 'in the real world' in my title. Can I in conclusion draw your attention to a recent development which, in my view, is a more realistic approach to the evaluation of different selection programmes than we have had previously? I have earlier in this lecture for instance spoken about maximisation of genetic gain at the limit. But who cares about gain at the limit? We are mostly interested in gain in a finite number of generations. Choices between selection programmes are then equivalent to choices between different investment alternatives. The standard method used for this is what is called 'discounted cash flow'. One assumes a specific notional rate of interest, usually taken as something of the order of 10%, and argues that on this basis having 100 dollars today is equivalent to having 110 dollars in a years time or 121 in two years time. Put the other way around 100 dollars available in two years time is then equivalent to 83 dollars in my hands today. Investment in any breeding programme has then in its three elements, looked at from this point of view. These are

(i) An initial capital investment,

(ii) An annual expenditure, which one generally assumes constant in all years, and

(iii) Genetic improvement which after a certain lag can be assumed to increase linearly with time.

It is then possible to discount expenditures and incomes which one expects to happen at various times in the future, and, summing these over say the next 20 years, to obtain a reasonable evaluation of discounted profits. The introduction, in a logical and elegant way, of economic values into our breeding decisions presents us then with a completely new dimension in animal breeding theory.
DR. ALAN ROBERTSON - "THE STATE OF QUANTITATIVE GENETICS IN RELATION TO THE REAL WORLD"

STERLING MUNRO: If redundant DNA is confined in its effect to intracellular function, might it not be concerned with cell survival and hence with animal livability?

ROBERTSON: On most recent evidence, the highly redundant DNA is apparently concentrated somewhere in the centromeric region of the chromosomes. It may therefore have a function in chromosome movement in cell division. A very surprising conclusion is that this DNA is a repeat of a very small number of basis indeed (6 in the case of the guinea pig). How it managed to get onto all chromosomes is a mystery.

JOHN GILL: In economic species, could one hope to distinguish between the optimum model and the heterozygosity model by evaluating the linearity co-linearity of inbreeding depression?

ROBERTSON: I would think not in that on the simple versions of the two models the inbreeding depression on fitness would be linear with inbreeding coefficient.

RICHARD FRAHM: When you were determining the genetic effects of each chromosome, were you able to measure the relative contribution of each chromosome to the total additive variation for that trait and if so did you find that this contribution was proportional to the relative size of the chromosome in the genome?

ROBERTSON: In our experiments we consistently find that the third chromosome has a greater contribution to the selection response than does the second, though the two are of roughly the same length. Their relative contributions to the additive genetic variance at the beginning we have never measured. The X-chromosome
which is about one half the size, contributes less than the other two chromosomes to selection response.

REID McCLELLAN: When you change scale, what genetic effects are you eliminating?

ROBERTSON: Hopefully we are trying to eliminate those epistatic effects due to being on the wrong scale. The kind of criterion I use is in essence to find that scale in which the deviations from additive models are at a minimum.

THEODORE B. BAILEY, JR.: In which species other than Drosophila is there evidence that a small number of loci (genes) may account for a large amount of the genetic variation?

ROBERTSON: There is some evidence from Allard's group and from work in Cambridge on wheat, using chromosomal interchanges, that some characters of economic importance are due to locatable loci.

DON KRESS: With reference to your result that 80-90% of the difference between the high and low lines was accounted for by approximately 10 loci; (i) how do you define a locus, (ii) do you think a similar result is likely in mammals with a larger number of loci and of chromosomes.

ROBERTSON: As always, a locus is a truly operational entity and the limits of resolution depend on how many potential cross-over chromosomes I am energetic enough to look at. As to the situation in other species my own prejudices are that we will again find this kind of a situation.

JACK HILL: Please relate your findings to the use of a selection index?

ROBERTSON: I think there is a great deal still to be learned about the practical use of selection indices. I am less prejudiced against them than I used to be though I am still unhappy to be using complicated machinery without any clear understanding of how complicated I need to be.
R. W. TOUCHBERRY: When you speak of crosses such as LLHL x LLLL and artificial selection within such crosses, would you not have to select within a large number of different kinds of crosses to prevent a given set of disequilibrium conditions from determining your results? If so, how many kinds of such crosses did you study?

ROBERTSON: Our crosses are all derived from the same two populations selected in different directions. I have studied all four of the possible combinations that one can make, having the third chromosomes segregating in high and low first, second and fourth backgrounds respectively and then the first, second and fourth chromosomes segregating in high and low third chromosome backgrounds.

ARNE NORDSKOG: Your LLHL x LLLL experiment seems to prove the optimum model interpretation. Early your papers seem to reject this model on the basis that it eventually would lead to zero genetic variance. You therefore favoured the heterozygous model.

ROBERTSON: I may not have explained the experimental results clearly. I would take it that as the segregating populations did not show any tendency to return towards the usual wild type values, this did not suggest any interaction between the bristle loci in their effect on fitness and I would interpret this as favouring the heterozygous rather than the optimum model.

FRANK ENFIELD: What methods do you suggest would be useful in looking for the major genes for important traits in economic species?

ROBERTSON: I would think that in poultry in which we have only six major chromosomes and a fair number of markers available as well as lines differing considerably in various metric traits, it would be possible to detect associations between specific chromosomes and metric characters. The trick which is very useful in Drosophila and which one lacks in poultry is that one can pass chromosomes
through males and have them retain their identity because of the absence of crossing over.

GORDON DICKERSON: Isn't universal pleiotropy qualified by limitation of specific gene action to certain biochemical or developmental steps or sites?

ROBERTSON: The experimental evidence on the effect of given gene substitutions on substrate pools in organisms like nurospora would suggest that a particular substitution generally affects a great many aspects of the organism. A worker in the Edinburgh Institute has recently been trying to discover what is the primary biochemical lesion in the gene obese in mice. The result of two years intensive biochemical work was that he really had very little clue because so many things were different in the obese mice from the normal. In general of course the word 'pleiotropy' means "I am surprised that a gene can affect these two characters". No-one is really surprised that the effect of a given gene on the length of the left leg is the same as its effect on the length of the right leg yet in a quantitative context we would certainly call this pleiotropy. We have to remember that quantitative geneticists deal with measurements and not characters.

RICHARD FRANKHAM: Wouldn't the best method for looking for large gene effects in domestic animals be to use Spickett's method of redefining the character in a more physiological manner?

ROBERTSON: In our methods of looking for loci we are essentially making a lot of crossover chromosomes in a certain region and examining their effects on a metric character. The break down of the character is equivalent in some ways to looking for pleiotropic effects of the loci - for other methods of making the classification. I have in fact found it most useful in such work.

RICHARD FRANKHAM: One has to be careful in looking at correlated traits as a means of identifying genes of large effect in commercial species as R. W. Davies from Cambridge has results that correlated response to selection in Drosophila
may be predominantly due to linkage effects.

ROBERTSON: I do not see that one can distinguish in this between effects due to linkage that a particular gene affecting another metric character has become fixed because it is on a particular chromosome with an effect on the metric character which is being made homozygous from the effect of drift at loci affecting other characters. But I have no direct experimental evidence on this point.